REMARKS

1. Overview of Claim Amendments

1.1. Claim 1 has been amended to require that

> (1) the method modulates the interaction between an FGF receptor (not merely an FGF receptor variant) and a polypeptide;
>
> (2) the polypeptide comprise a binding site for the receptor and binds to the receptor,
>
> (3) the polypetide comprises SEQ ID NO:9 (note that SEQ ID NO:9 is known to comprise a binding site for FGFR1),
>
> (4) the compound is either (I) a peptide, of specified structure, with a length of 6-16 amino acids, or (II) a multimer comprising a plurality of peptides of the specified structure,
>
> (5) the specified structure of the peptide, as referred to above, and thus also of the monomeric units of the contemplated multimer, is that it (a) comprises an amino acid sequence at least 80% identical to SEQ ID NO:9, or (b) is a fragment, at least six amino acids in length, of (a).

Basis for the compound being a peptide is at e.g. original claim 17. The basis for the limitation of 6-16 residues is at page 29, lines 1-3.

The amended claim also permits variants at least 80% identical to SEQ ID NO:9 (which itself is of course 100% identical to SEQ ID NO:9, and thus covered by (a)). Basis for "80% homology" appears at page 27, line 22. Homology is defined at page 27, lines 27-29 as equivalent to identity, so the claim recites 80% identical, the PTO having expressed a preference in the past for avoiding the term "homology". Note that % homology is defined in such manner that a fragment of a predetermined sequence such as SID 9 is considered to have 100% homology with the predetermined sequence. Page 27, lines 19-20.

Clause (b) permits fragments of SID 9. Since SID 9 is itself 14 residues, the teaching of 6-16 residues clearly means that the compound may be a fragment of SID9, and this is explicitly taught at page 27, lines 9-11. To meet the "6-16" limitation, the fragment must of course be at least 6 a.a. long.

Clause (b) also permits fragments of the aforementioned variants of SID9. This is based on the teaching at page 27, lines 9-15, i.e., the fragment may be "derived" from SID 9, and such derivation can clearly encompass mutation.

Coverage of multimers is based on page 27, line 33 to page 28, line 6; page 29, lines 920, and page 67, lines 11 to 27.

Claims 72-79 are directed to various subsets of the compounds of claim 1, clauses (I) and (II).

1.2. The nested limitation of claim 15 has been moved to new claim 58.

1.3. The more stringent percentage identity claims 61-62 are based on page 27, line 23. Claim 71, requiring at least 95% positive amino acid matches as defined at page 27, lines 29-33, is based on page 27, line 26.

1.4. With regard to the multimer-specific claims, basis for claims 63-66 is at page 29, lines 9-20, and for claims 67-70 at page 27, line 33 to page 28, line 6.

1.5. Certain peptides are recited in claims 20, 59, 60 or 80-84, and their homology with SID 9 is shown below.

	a.a matches	% homology (identity) in claims 20, 59, 60 and 80-84
TIMGLKPETRYAVR	(SEQ ID NO: 9)	100
TLLGLKPDTTYDIK	(SEQ ID NO: 78) 12/14	86
TVSGLKPGTRY	(SEQ ID NO: 82) 09/11	82
TISGLKPDTTY	(SEQ ID NO: 83) 09/11	82

TLQGLKPDTAY	(SEQ ID NO: 84)	09/11	82
LRGLKPWTQYAV	(SEQ ID NO: 85)	11/12	92
LQGLKPWTQYAI	(SEQ ID NO: 87)	10/12	83
GLKPWTQYAV	(SEQ ID NO: 89)	09/10	90
TLASLKPWTQYAV	(SEQ ID NO: 90)	11/13	85
LMGLQPATEYIV	(SEQ ID NO: 91)	10/12	83
TLTGLKPDTTYDVK	(SEQ ID NO: 93)	12/14	86
TSGLQPETSYSL	(SEQ ID NO: 94)	10/12	83
TLLGLKPDTTYDIK	(SEQ ID NO: 95)	12/14	86
in claim 59, 60 only			
TVTGLKPETSYMVK	(SEQ ID NO: 75)	11/14	79
TLQGLRPETAYELR	(SEQ ID NO: 79)	11/14	79
TLRGLRPETAYELR	(SEQ ID NO: 80)	11/14	79
TLMNLRPKTGYSVR	(SEQ ID NO: 81)	11/14	79
TLMNLRPKTGYSVR	(SEQ ID NO: 132)	11/14	79

Amino acids marked dark grey are identical matches, amino acids marked light grey are positive amino acid matches. A positive amino acid match is defined at page 16, lines 9-14.

SID 78, 82-85, 87, 89-91, and 93-95 are covered by claim 1 because they are variants which satisfy the 80% minimum identity limitation of 1(b).

SID 75 is covered by claim 1(b) because it comprises a six amino acid fragment (GLKPET) which is a six amino acid fragment of SID 9.

SID79 and 80 are covered by claim 1(b) because they comprise a six amino acid fragment (GLRPET) of the variant TIMGLRPETRYAVR which is 13/14 (92.9%) identical to SID 9. (Also note that this fragment is 83% identical to GLKPET which is a six amino acid fragment of SID 9.)

SID81 and 132 are covered by claim 1(b) because they comprise a six amino acid fragment (TGYSVR) of the variant TIMGLKPETGYSVR, which is 12/14 (85.7%) identical to SID 9.

1.6. Claims 86-89 further define the FGFR, with basis as set forth in section 4.1. For "human", see also the human diseases recited at pp. 54-61.

2. Formal Matters

2.1. Unity (OA §§1-2)

2.1.1. Applicants ratify the provisional election of FGFR1 (see OA page 4, third full paragraph).

2.1.2. With regard to the species restriction, the examiner says In re Harnisch is applied in deciding wether a species restriction among the members of a Markush group is proper. Harnisch was a domestic restriction case, whereas this case is subject to PCT practice. The relevant PCT practice is in the PCT administrative instructions, Annex B, part 1, para. (f).

Even if Harnisch applied, there is some structural similarity among FGF receptors (see Exhibit A attached to election with traverse), and FGF receptors have common utility despite some cell specificity.

The Examiner concedes that there is some homology among the peptide compounds SID 2-146 but not that there is "common structure".

But it is quite evident that at least some of the peptide compounds SID 2-8, 10-146 indeed shared a common structure with SID 9. Referring to Exhibit B of the election, SID9 has six contiguous amino acids, and nine total amino acids, in common with SID75. That would appear to be a common structure. Many more of the sequences of Ex. B have at least a contiguous tetrapeptide in common with SID9.

Claim 1, as amended, requires that the variant peptides be at least 80% identical to SID 9. The minimum peptide length is six amino acids, and it is well known in the art that hexapeptide sequences can act as binding sites.

2.1.3. We respectfully assert that the amendments to claim 1 overcome the a posteriori holding of lack of unity over Skladchikova. Hence, we should be entitled to coverage of FGF receptors other than the elected FGFR1 and of the claimed variants and fragments of the elected peptide SID9. In particular, the peptides set forth in claims 20, 59, 60 and

80-84 (all of which were listed on Ex. B to the election with traverse filed November 13, 2007 as being especially appropriate for rejoinder), should be rejoined. The homology of these peptides with SID9 is apparent from the table in section 1.5.

Claim 20 should in any event be rejoined (and new claims 59, 60, and 80-84 joined) because they all recite the elected peptide SEQ ID NO:9.

2.1.4. We have amended method of treatment claim 55 so it has a combination/subcombination relationship to claim 1. If claim 1 is deemed allowable, claim 55 should be rejoined.

2.1.5. We note that the examiner has conflated the polypeptide (which interacts with the receptor) and the compound, which can be a peptide as in the case of SID 2-146, which modulates that interaction.

In the discussion of the restriction in the present action, the examiner refers to the elected peptide on page 2, but to the "recited polypeptides set forth in SEQ ID NOS: 2-146" on page , and to the elected "polypeptide" on page 4. It is the peptide modulatory compound, not the modulated polypeptide, which was the direct subject of the restriction/election.

The restriction asked us to elect a "peptide" which we took to mean an election of one of the peptides which form a subset of the contemplated modulatory compounds. We elected SEQ ID NO:9.

In making this election, we explained (section 4) that SEQ ID NO:9 is the FGFR binding motif of NCAM (specifically, it is residues 573-586 of NCAM F3 module 1, see page 67, lines 5-10), and thus that we were entitled to examination of the claims vis-a-vis polypeptides, such as NCAM, which comprise SEQ ID NO:9 (and hence would have their interaction with FGFR modulated by SID9). This could be considered an implicit election of polypeptides **comprising** SID 9, but we wish to remind the examiner that the polypeptides aren't SID 9, per

se. We think that the examiner realized this at the time he reviewed the election (he examined claim 8, reciting NCAM), but we thought we should point out the ambiguity which was starting to creep into the record. The terms "polypeptide" and "peptide" should not be confused.

2.2. Sequence Compliance; Drawings (OA §§3-4)

We have submitted a substitute sequence listing which includes the sequences shown in Figs. 6, 8 and 10, and amended the specification to provide the appropriate identifications.

Applicants hereby submit the following:

a paper copy of a "Sequence Listing", complying with §1.821(c), to be incorporated into the specification as directed above;

the Sequence Listing in computer readable form, complying with §1.821(e) and §1.824, including, if an amendment to the paper copy is submitted, all previously submitted data with the amendment incorporated therein;

The undersigned attorney or agent hereby states as follows:

(a) this submission does not include new matter [§1.821(g)];

(b) the contents of the paper copy (as amended, if applicable) and the computer readable form of the Sequence Listing, are the same [§1.821(f) and §1.825(b)];

(c) if the paper copy has been amended, the amendment is supported by the specification and does not include new matter [§1.825(a)]; and

(d) if the computer readable form submitted herewith is a substitute for a form found upon receipt by the PTO to be damaged or unreadable, that the substitute data is identical to that originally filed [§1.825(d)].

2.3. Minor Informalities (OA §12)

The second limitation of claim 15 was deleted so the complaint that it did not recite Kd units is moot.

Applicants have traversed the restrictions among fibroblast growth receptors and binding polypeptides and hence the claims may continue to cover non-elected species. If a generic claim is deemed allowable, rejoinder will be proper under PCT practice, see 1.1 above. However, Applicants have cancelled or amended those claims which covered species excluded by amended claim 1 or which do not further limit claim 1.

3. Definiteness (OA §8-9)

3.1. We have amended claim 15 to strike the nested narrow range, which is now recited in new claim 58.

3.2. We have cancelled claim 18, without prejudice or disclaimer.

3.3. The Examiner questions the terminology "modulating the interaction", and, in particular, whether "interaction" encompasses something besides "binding". Binding is of course a form of interaction.

The term "interaction" is defined at page 13, lines 13-14, and should be interpreted in view of the discussion at page 12, line 2 to page 13, line 11.

It can bee seen that the "interaction" requires "contact", which we consider to be synonymous with "binding". However, the contact may be indirect. Thus, if molecule A causes the release of molecule B, which in turn binds cell surface receptor R, then both A and B are "interacting" with R.

4. Written Description (OA §§6, 7)

Claim 1, as examined, recited modulation of the interaction of

(1) a functional cell surface fibroblast growth receptor,

or a variant thereof

and

(2) a polypeptide having a binding site to said receptor, wherein said binding site comprises one of the sequences set forth in SEQ ID NOs:2-146,

by means of

(3) a compound capable of interacting with the receptor at the binding site of the receptor for the polypeptide.

The Examiner questions whether there is adequate written description for the "genus of FGFR1 variants and their binding peptides".

4.1. Claim 1 has been amended to strike the term "or a variant thereof". We believe that the known fibroblast growth factors, FGFR1-FGFR4, are fairly deemed to be representative of the genus of "fibroblast growth factor receptors" as now recited by claim 1.

Mouse FGFR1 sequence p16092 is cited on page 62, line 34. The FGFR sequences cited in the specification at page 20, line 29 to page 21, line 4 are

FGFR1:
Q9QZM7 (mouse, 733 aa)
Q99AVV7 [this appears to contain a typo]
Q9UD50 (human fragment, 279 aa)
Q63827 (rat, 729 aa)

FGFR2:
Q96KM2 (human, 821 aa)
P21802 (same as Q96KM2)
Q63241 (rat fragment, 330 aa)

FGFR3:
Q95M13 (bovine, 802 aa)
AF487554 (human fragment 769 or 771 aa)
Q99052 (mouse, 800 aa)

FGFR4:
Q91742 (Xenopus laevis, 818 aa).

Currently, known FGFR1 sequences include the mature forms of various mouse (e.g., P16092) and human (e.g. P11362) precursor sequences. Known FGFR2 similarly include mouse (AIYYN9) and human (P21802) sequences. Known FGFR3 similarly include mouse (Q7TSI8) and human (P22607) sequences. Known FGFR4 similarly include mouse (Q03142) and human (P22455).

Using P16092 as a query sequence for a BLASTP search[1], we found the following matches (among others):

Protein (precursor of)	% Identity	% Positive
Human FGFR1 (P11362)	98	99
Rat FGFR1 (Q04589)	98	99
Sumatran orangutan FGFR1 (Q5R8Q3)	97	98
Bovine FGFR1 (A4IFL5)	98	98
Chicken FGFR1 (P21804)	91	95
African Clawed Frog FGFR (Q91897)	79	90
Zebrafish FGFR1 (Q90Z00)	73	85
Human FGFR2 (P21802)	71	82
Chicken FGFR2 (P18461)	71	82
Mouse FGFR2 (A1YYN9)	71	83
Chicken FGFR3 (P18460)	69	81
Zebrafish FGFR3 (Q9I8X3)	64	78
Rat FGFR3 (Q9JHX9)	63	77
Mouse FGFR3 (Q7TSI8)	63	77

Powers et al., (2000) "Fibroblast growth factors: their

[1] Search conducted online through www.expasy.ch/tools with default matrix and gap penalties, and BLAST low complexity region FILTER off.

receptors and signaling", Endocrine-Related Cancer, 7:165-197 (IDS Ref. 19) is cited at P. 2, L21-23 and P11, 31-32. In Figure 1, he compares human FGFR1 with human FGFR2, 3 and 4, at the amino acid level, on a domain-by-domain basis. Given our showing that SEQ ID NO:9 comprises the binding site for NCAM F3 versus FGFR1 Ig module 3 and FGFR1 combined Ig modules 2 and 3 (page 62, line 34 to page 63, line 4; page 64, line 33 to page 65, line 5; page 66, lines 21-24 and 33-35), it follows that we are most interested in the Ig modules 2 and 3. The homology of human FGFR1 for these domains in the other human FGFR's is as follows:

	FGFR2	FGFR3	FGFR4
Ig2	79%	64%	61%
Ig3	78%	81%	74%

The technical note on page 38 of the Written Description Training Materials (Revision 1, March 26, 2008) indicates that generally speaking, up to 50% substitution can be tolerated before the original tertiary structure is lost. With respect to the Ig3 domain, the degree of substitution in FGFR2, 3 and 4, relative to 1, does not exceed 26%.

4.2. Likewise, the examiner questions WD for the elected polypeptides comprising the sequence of SEQ ID NO:9, absent any further limitation as to structure or functional activity.

Claim 1, as examined, recited modulation of the interaction of the polypeptide with the receptor. This plainly implies that in the absence of the modulatory compound, the polypeptide interacts with the receptor. Such is a functional limitation. Moreover, claim 1 recited that the polypeptide comprised a "binding site to said receptor", which we respectfully suggest is a more specific functional limitation on the nature of the interaction.

The Written Description Training Materials (Revision 1, March 25, 2008), Example 9, indicated that the model claim "An isolated protein comprising the amino acid sequence shown in

SEQ ID NO:3" satisfied the written description requirement.

Applicants demonstrated that the NCAM F3 modules 1, 2 bind directly to FGFR modules 2, 3, see Example 2 on page 66.

Applicants identified, by NMR, the specific residues involved in NCAM F3 binding to FGFR, see Example 1 on pages 63-66.

Applicants confirmed the prediction that NCAM's FGFR and ATP binding sites overlapped by showing that ATP inhibited NCAM:FGFR binding, see pp. 66-67.

Applicants then showed that peptides corresponding to the EF loop (SEQ ID NO:9) of F3 module 1 and FG loop (SEQ ID NO:1) of the F3 module 2, when provided in dendrimeric form, bound FGFR in a manner detectable by SPR (page 67).

Further experiments by Applicants explored the biological activity of the FG loop peptide and in some cases also the EF loop peptide, see pp. 69-71.

Since at least two polypeptides comprising SEQ ID NO:9 (NCAM, F3, and the dendrimeric SID 9) have been shown to bind FGFR, Applicants respectfully submit that a claim reciting interaction with a polypeptide comprising the sequence of SID 9 is proper.

To avoid any doubt, we have amended the claim to explicitly require that "said polypeptide binds said receptor".

5. Prior Art (OA §§10-11)

The examined claims (1, 4, 5, 8, 14, 15, 17, 18) are rejected as anticipated by Skladchikova (1999).

Claim 1 is directed to a method of modulating the interaction between an FGF receptor (or variant thereof) and a polypeptide of SEQ ID NO:2-146, by providing an appropriate compound which interacts with the receptor. The claim was examined on the basis of the receptor being FGFR1 and the polypeptide being SID 9 (14 a.a.; TIMGLKPETRYAVR), which is the FGFR binding motif in the FIII-1 domain of NCAM.

Claim 17 requires that the compound be a peptide, and 18, that it "comprises" 6-16 contiguous AAs of one of certain sequences, as examined, presumably, SID 9.

The Examiner asserts that Skladchikova teaches that NCAM interacts with FGFR by means of NCAM FIII-1 domain, which inherently comprises SEQ ID NO:9.

At page 11, lines 1-8, the Examiner says:

> Skladchikova et al. teach modulation of NCAM-FGFR interaction with a fragment of FGFR (the FGFR-CAM homology domain or CHD), an anti-FGFR antibody, an anti-NCAM antibody (an antibody against the NCAM-Fn-III 1-2modules), as well as ATP in hippocampal neuronal cultures that necessarily express FGFR1 (page 212, last paragraph of left column to the 1st paragraph of right column; Fig. 10). FGFR antibodies, CHD, and NCAM antibodies all abrogated ATP-stimulated neurite outgrowth (page 212, the 1st paragraph of right column; Fig. 10).

Most of the claims, as examined, permitted the "compound" to be NCAM itself, or Skladchikova's antibody. (Unless "peptide" implies an upper limit on size, claim 17 would have read on NCAM and the antibody, too. Claim 18 excluded the antibody but, by virtue of "comprising", still reads on NCAM.

There is no discernible homology between Skladchikova's CHD peptide (which if we are reading the article correctly, is a fragment of the FGF receptor) and our SID 9 (an NCAM fragment).

We have amended claim 1 to recite that the compound is

> (I) a peptide of 6-16 amino acid residues, and comprises (a) an amino acid sequence at least 80% identical to SEQ ID NO:9, or (b) a fragment, at least 6 a.a. in length, of (a), or
>
> (II) a multimer comprising a plurality of monomers, each monomers being independently a peptide of (I);

We believe this avoids anticipation. Skladchikova's

antibody, the CHD peptide (20 a.a.; VAPYWTSPEKMEKKLHAVPA), and NCAM are neither a 6-16 a.a. peptide, nor a multimer of SID9.

We additionally observe that the CHD peptide does not comprise SEQ ID NO:9, nor does it appear on inspection to satisfy clauses (I)(b) or (I)(c) of claim 1, that is, it does not comprise a variant sequence at least 80% identical to SEQ ID NO:9 (TIMKGLKPETRYAVR), and it does not appear to comprise a sequence of at least six amino acids which is a fragment of such a variant. Indeed, the longest continuous subsequence which the two peptides have in common appears to be a dipeptide (PE or AV). LALIGN found no homology between SID9 and the CHD peptide:

align output for Our SID9 vs. CHD
[ISREC-Server] Date: Fri Jul 18 21:00:37 2008

ulimit -t 30; /usr/molbio/bin/lalign -f -14 -g -4 -s /usr/molbio/share/fasta3/blosum62.mat ./wwwtmp/.6360.1.seq ./wwwtmp/.6360.2.seq 3 > ./wwwtmp/.6360.out LALIGN finds the best local alignments between two sequences version 2.1u09 December 2006 Please cite: X. Huang and W. Miller (1991) Adv. Appl. Math. 12:373-381 alignments < E(0.05):score: -1 (50 max)

Comparison of:
(A) ./wwwtmp/.6360.1.seq Our SID9 15 bp
- 15 aa
(B) ./wwwtmp/.6360.2.seq CHD 20 bp
- 20 aa
using matrix file: /usr/molbio/share/fasta3/blosum62.mat (11/-4), gap-open/ext: -14/-4 E(limit) 0.05

There has been no showing of any homology between the antibody and SEQ ID NO:9, and there is no reason to expect such homology because SEQ ID NO:9 is derived from an

immunoglobulin.

5. Miscellaneous

5.1. It has come to our attention that the preliminary amendment filed April 5, 2008, did not fully comply with the formal requirements of 37 CFR 1.121(c) vis-a-vis the use of status identifiers and the marking to show changes. Specifically

-claim 35: marked currently amended, but was not amended.
-claim 41:"claim 39" added but not underlined.
-claims 40 & 43: added "2" but not underlined.

We hope that this explanation is sufficient to clarify the record, but on request we will submit a substitute claims section for the April 5, 2008 preliminary amendment.

5.2. We note that we previously overlooked that withdrawn claim 45 was multiply dependent on claims 25 and 43. This claim has now been cancelled. If we nonetheless must pay the fee for first presentation of a MD claim, please charge it to Deposit Account 02-4035.

Respectfully submitted,

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Enclosure
-Sequence Listing (paper/PDF and CRF/TXT)

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G:\ipc\g-i\hoib\BOCK8\bock8.pto amendment.wpd